Dibenzodiazepine derivatives, their preparation and use

Description

The present invention relates to novel dibenzodiazepine derivatives, to their preparation and to their use, as inhibitors of the enzyme poly(ADP-ribose) polymerase or PARP (EC 2.4.2.30), for preparing pharmaceuticals.

Poly(ADP-ribose) polymerase (PARP), or, as it is also termed, poly(ADP-ribose) synthase (PARS), is a regulatory enzyme which is found in cell nuclei (K. Ikai et al., J. Histochem. Cytochem. 1983, 31, 1261-1264). It is assumed that PARP plays a role in the repair of DNA breaks (M.S. Satoh et al., Nature 1992, 356, 356-358). Damage to, or breaks in, the DNA strands activate the PARP enzyme which, when it is activated, catalyses the transfer of ADP-ribose from NAD (S. Shaw, Adv. Radiat. Biol., 1984, 11, 1-69). At the same time, nicotinamide is released from the NAD. Other enzymes then reconvert nicotinamide into NAD, with this process consuming the energy source ATP. Accordingly, high activation of PARP would result in an unphysiologically high consumption of ATP, with this leading, in the extreme case, to cell damage and cell death.

It is known that free radicals, such as superoxide anion, NO and hydrogen peroxide can give rise to DNA damage in cells and thereby activate PARP. The formation of large quantities of free radicals is observed in a number of pathophysiological states and it is assumed that this accumulation of free radicals leads or contributes to the observed cell or organ damage. These pathophysiological states include, for example, ischemic states of organs, as in stroke and cardiac infarction (C. Thiemermann et al., Proc. Natl. Acad. Sci. USA, 1997, 94, 679-683), or ischemia of the kidneys, or else reperfusion damage as occurs, for example, following the lysis of cardiac infarction (see above: C. Thiemermann et al). Consequently, inhibition

of the PARP enzyme could be a means of at least partially preventing or alleviating this damage. PARP inhibitors could consequently constitute a novel therapy principle for treating a number of diseases.

The PARP enzyme exerts an influence on the repair of DNA damage and could consequently also play a role in the therapy of cancer diseases, since a higher potential activity towards tumour tissue has been observed in combination with cytostatically active substances (G. Chen et al. Cancer Chemo. Parmacol. 1988, 22, 303).

Non-limiting examples of tumours are leukaemia, glioblastomers, lymphomas, melanomas and mammary and cervical carcinomas.

It has furthermore been found that PARP inhibitors are able to exhibit an immunosuppressive effect (D. Weltin et al., *Int. J. Immunopharmacol.* 1995, 17, 265-271).

It has also been discovered that PARP is involved in immunological disorders or diseases, such as rheumatoid arthritis and septic shock, in which the immune system plays an important role and that PARP inhibitors are able to exhibit a beneficial effect on the course of the disease (H. Kröger et al. *Inflammation* 1996, 20, 203-215; W. Ehrlich et al. *Rheumatol. Int.* 1995, 15, 171-172; C. Szabo et al., *Proc. Natl. Acad. Sci. USA* 1998, 95, 3867-3872; S. Cuzzocrea et al. *Eur. J. Pharmacol.* 1998, 342, 67-76).

Within the meaning of this invention, PARP is also understood as meaning isoenzymes of the above-described PARP enzyme.

Furthermore, the PARP inhibitor 3-aminobenzamide displayed protective effects in a model of circulatory

shock (S. Cuzzocrea et al., *Br. J. Pharmacol.* 1997, 121, 1065-1074).

There are also experimental indications that inhibitors of the PARP enzyme could be of use as a means for treating diabetes mellitus (V. Burkart et al. *Nature Med.* 1999, 5, 314-319).

Experimental indications also show that PARP inhibitors could be of use as a means for treating viral infections, in particular infections with retroviruses (J.A. Gäken et al. *J. Virol.* 1996, 70, 3992-4000; M. Kameoka et al. *Biochem Biophys Res Commun* 1999, 262, 285-9).

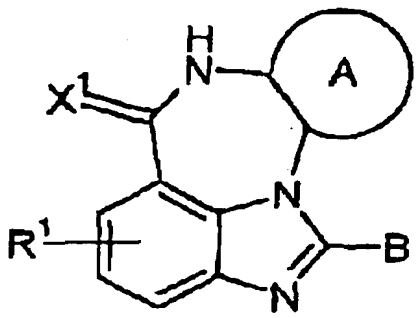
Dibenzodiazepines and dibenzodiazepinones and their derivatives are a chemical class which has been frequently used in organic synthesis. However, derivatives of these compounds which additionally carry a fused-on imidazo ring, that is imidazodibenzodiazepinones, have not been described.

The compounds according to the invention, of the general formula I, have not hitherto been described and are consequently novel.

It has furthermore been found, surprisingly, that dibenzodiazepine derivatives which carry a fused-on ring are very effective inhibitors of the PARP enzyme.

The present invention describes novel dibenzodiazepine derivatives of the general formula I which are potent inhibitors of PARP.

The present invention relates to substituted dibenzodiazepine derivatives of the general formula I



I

in which

A can be a saturated, unstaturated or partially unsaturated ring having at most 6 carbon atoms, an unsaturated or partially unsaturated ring having at most 5 carbon atoms and from 0 to 3 nitrogen atoms, from 0 to 2 oxygen atoms and/or from 0 to 2 sulphur atoms, and

X^1 can be S, O and NH, and

R^1 denotes hydrogen, chlorine, fluorine, bromine, iodine, branched and unbranched C_1-C_6-alkyl, OH, nitro, CF_3, CN, $NR^{11}R^{12}$, NH-CO-R^{13}, or O-C_1-C_4-alkyl, where R^{11} and R^{12}, independently of each other, denote hydrogen or C_1-C_4-alkyl, and R^{13} denotes hydrogen, C_1-C_4-alkyl, C_1-C_4-alkylphenyl or phenyl, and

B can denote an unsaturated, saturated or partially unsaturated mono-, bi- or tri-cyclic ring having at most 15 carbon atoms or an unsaturated, saturated or partially unsaturated mono-, bi- or tri-cyclic ring having at most 14 carbon atoms and from 0 to 5 nitrogen atoms, from 0 to 2 oxygen atoms and/or from 0 to 2 sulphur atoms, which are in each case additionally substituted by one R^4 and at most 3 different or identical R^5 radicals, and one or two carbon, or sulphur, atoms can also carry one or two =O groups, such as keto groups,

sulphones or sulphoxides, or denotes a radical L_v-Y-M_w, in which

L can be a straight-chain or branched saturated or unsaturated carbon chain of from 1 to 8 C atoms, where each carbon atom can be substituted by one or two R^4 radicals and at most two different or identical R^5 radicals, and

M possesses, independently of L, the same meaning as L, and

Y denotes a bond or can be S, O or NR^3, where R^3 is hydrogen, branched or unbranched C_1-C_6-alkyl, C_1-C_4-alkylphenyl or phenyl, and

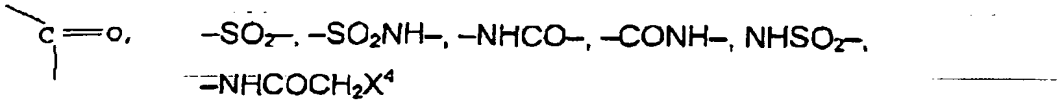
v can denote 0 and 1, and

w can be 0 and 1, and

R^4 denotes hydrogen and $-(D)_p-(E)_s-(F^1)_q-G^1-(F^2)_r-G^2-G^3$, where

D is S, NR^{43} and O,

E is phenyl,



and

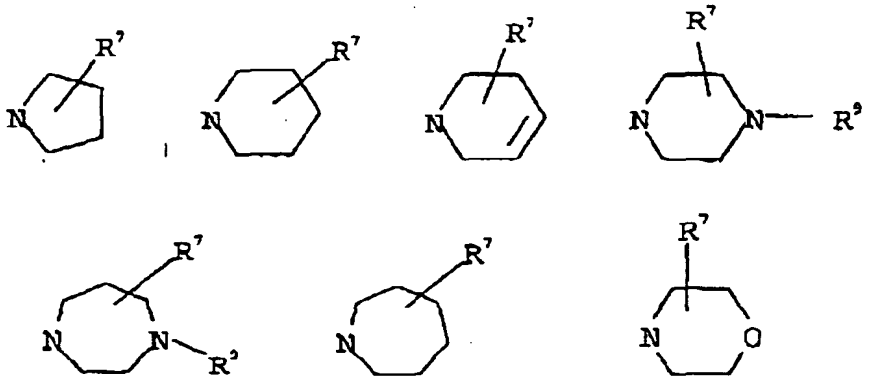
X^4 can denote S, O or NH, and

F^1 can be a straight-chain or branched, saturated or unsaturated carbon chain of from 1 to 8 C atoms and

F^2 independently of F^1, possesses the same meaning as F^1,

G^1 denotes a bond or can denote an unsaturated, saturated or partially unsaturated mono-, bi- or tri-cyclic ring having at most 15 carbon atoms or an unsaturated, saturated or partially unsaturated mono-, bi- or tri-cyclic ring having at most 14 carbon atoms and from 0 to 5 nitrogen atoms, from 0 to 2 oxygen atoms and/or from 0 to 2 sulphur atoms, which are in each case additionally substituted by at most 3 different or identical R^5 radicals, and one or two carbon, or sulphur, atoms can also carry one or two =O groups, and

G^2 denotes $NR^{41}R^{42}$ and



or a bond, and

G^3 can denote an unsaturated, saturated or partially unsaturated mono-, bi- or tri-cyclic ring having at most 15 carbon atoms or an unsaturated, saturated or partially unsaturated mono-, bi- or tri-cyclic ring having at most 14 carbon atoms and from 0 to 5 nitrogen atoms, from 0 to 2 oxygen atoms and/or from 0 to 2 sulphur atoms, which are in each case additionally substituted by at most 3 different

or identical R^5 radicals, and one or two carbon, or sulphur, atoms can also carry one or two =O groups, or denotes hydrogen, and

p can denote 0 and 1, and

s can be 0 and 1, and

q can be 0 and 1, and

r can be 0 and 1, and

R^{41} can be hydrogen, C_1-C_6-alkyl, where each carbon atom can additionally carry up to 2 R^6 radicals, phenyl, which can additionally carry at most 2 R^6 radicals, and $(CH_2)_t$-K, and

R^{42} can be hydrogen, C_1-C_6-alkyl, -CO-R^8, CO_2-R^8, SO_2NH_2, SO_2-R^8, -(C=NH)-R^8 and (C=NH)-NHR^8, and

R^{43} can be hydrogen and C_1-C_4-alkyl, and

t can be 1, 2, 3 or 4, and

K can be $NR^{11}R^{12}$, NR^{11}-C_1-C_4-alkylphenyl, pyrrolidine, piperidine, 1,2,5,6-tetrahydropyridine, morpholine, homopiperidine, piperazine, which can be additionally substituted by an alkyl radical C_1-C_6-alkyl, and homopiperazine, which can be additionally substituted by an alkyl radical C_1-C_6-alkyl, and

R^5 can be hydrogen, chlorine, fluorine, bromine, iodine, OH, nitro, CF_3, CN, $NR^{11}R^{12}$, NH-CO-R^{13}, C_1-C_4-alkyl-CO-NH-R^{13}, COR^8, C_0-C_4-alkyl-O-CO-R^{13}, C_1-C_4-alkylphenyl, phenyl, CO_2-C_1-C_4-alkyl and branched and unbranched C_1-C_6-alkyl, O-C_1-C_4-alkyl or S-C_1-C_4-alkyl where each C atom of the alkyl chains

can carry up to two R^6 radicals and the alkyl chains can also be unsaturated, and

R^6 can be hydrogen, chlorine, fluorine, bromine, iodine, branched or unbranched C_1-C_6-alkyl, OH, nitro, CF_3, CN, $NR^{11}R^{12}$, NH-CO-R^{13} or O-C_1-C_4-alkyl,

R^7 can be hydrogen, C_1-C_6-alkyl, phenyl, where the ring can be additionally substituted by up to two R^{71} radicals, and an amine $NR^{11}R^{12}$ or a cyclic saturated amine having from 3 to 7 members which can additionally be substituted by an alkyl radical C_1-C_6-alkyl, and homopiperazine which can be additionally substituted by an alkyl radical C_1-C_6-alkyl, and

where the radicals R^{11}, R^{12} and R^{13} in K, R^5, R^6 and R^7 can, independently of each other, assume the same meaning as R^1, and

R^{71} can be OH, C_1-C_6-alkyl, O-C_1-C_4-alkyl, chlorine, bromine, iodine, fluorine, CF_3, nitro or NH_2, and

R^8 can be C_1-C_6-alkyl, CF_3, phenyl or C_1-C_4-alkylphenyl, where the ring can additionally be substituted by up to two R^{81} radicals, and

R^{81} can be OH, C_1-C_6-alkyl, O-C_1-C_4-alkyl, chlorine, bromine, iodine, fluorine, CF_3, nitro or NH_2, and

R^9 can be hydrogen, C_1-C_6-alkyl, C_1-C_4-alkylphenyl, CO_2-C_1-C_4-alkylphenyl, CO_2-C_1-C_4-alkyl, SO_2-phenyl, COR^8 and phenyl, where the phenyl rings can be additionally substituted by up to two R^{91} radicals, and

R^{91} can be OH, C_1-C_6-alkyl, O-C_1-C_4-alkyl, chlorine, bromine, iodine, fluorine, CF_3, nitro or NH_2,

and also their tautomeric forms and possible enantiomeric and diastereomeric forms and their prodrugs.

Preference is given to compounds of the formula I where

A represents a benzo ring,

X^1 represents O, and

R^1 is hydrogen.

Preference is given to compounds of the formula I, as indicated above, in which

B can denote an unsaturated, saturated or partially unsaturated mono-, bi- or tri-cyclic ring having at most 15 carbon atoms, an unsaturated, saturated or partially unsaturated mono-, bi- or tri-cyclic ring having at most 14 carbon atoms and from 0 to 5 nitrogen atoms, from 0 to 2 oxygen atoms and/or from 0 to 2 sulphur atoms, which are in each case additionally substituted by one R^4 and at most 3 different or identical R^5 radicals, and one or two carbon, or sulphur, atoms can also carry one or two =O groups.

The following radicals are particularly preferred for B:

B phenyl, cyclohexyl, piperidine, pyridine, pyrimidine, pyrrole, pyrazole, thiophene, furan, oxazole, naphthalene, piperazine, quinoline or pyrazine, which radicals can additionally be substituted by one R^4 or at most 2 R^5.

Particular preference is given to compounds of the formula I where

R^4 denotes $D_{0,1}$-$F^1_{0.1}$-G^2-G^3 where G^3 is hydrogen, and

D denotes O and NR^{43}, where R^{43} is hydrogen and C_1-C_3-alkyl, and

F^1 denotes C_2-C_4-alkyl.

Preference is likewise given to compounds of formula I, where

R^4 denotes G^1-$F^1_{0.1}$-G^2-G^3 where G^3 is hydrogen, and

F^1 denotes C_1-C_2-alkyl.

Very particular preference is given to compounds of the formula I, where

R^4 denotes G^1-$F^1_{0.1}$-G^2-G^3 where G^3 is hydrogen, and

G^1 denotes imidazole or pyrrole which in each case can be additionally substituted by at most 3 different or identical R^5 radicals, and

F^1 denotes C_1-C_2-alkyl.

Preference is likewise given to compounds of the formula I as indicated above in which

B denotes a radical L_v-Y-M_w in which

L can be a straight-chain or branched, saturated or unsaturated carbon chain of from 1 to 8 C atoms, where each carbon atom can be substituted by one or two R^4 radicals and at most two different or identical R^5 radicals, and

M independently of L, possesses the same meaning as L, and

Y denotes a bond or can be S, O or NR^3, where R^3 can be hydrogen, branched and unbranched C_1-C_6-alkyl, C_1-C_4-alkyl-phenyl or phenyl, and

v can denote 0 and 1, and

w can denote 0 and 1.

Of these, particular preference is given to compounds of the formula I where

L can be a carbon chain of from 1 to 8 C atoms, which chain contains at least one triple bond, where the carbon atoms of the chain can be substituted by one or two R^4 radicals and at most two different or identical R^5 radicals, and

v denotes 1, and

w can denote 0 and 1.

The compounds of the formula I can be used as racemates, as enantiomerically pure compounds or as diastereomers. If enantiomerically pure compounds are desired, they can be obtained, for example, by carrying out a classical racemate resolution of the compounds of the formula I, or their intermediates, using a suitable optically active base or acid.

Alkyl chains may in each case be branched or unbranched. Unbranched alkyl chains are preferred.

The invention also relates to compounds which are mesomers or tautomers of the compounds of the formula I.

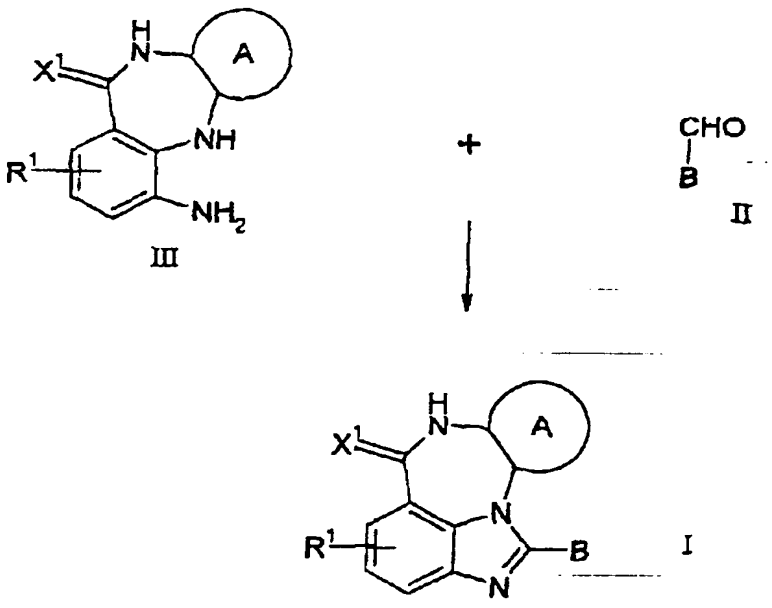
The invention furthermore relates to physiologically tolerated salts of the compounds I which can be obtained by reacting compounds I with a suitable acid

or base. Examples of suitable acids and bases are listed in Fortschritte der Arzneimittelforschung [Advances in drug research], 1966, Birkhäuser Verlag, Vol. 10, pp. 224-285. They include, for example, hydrochloric acid, citric acid, tartaric acid, lactic acid, phosphoric acid, methanesulphonic acid, acetic acid, formic acid, maleic acid, fumaric acid, etc., or sodium hydroxide, lithium hydroxide, potassium hydroxide, and Tris, respectively.

Prodrugs are understood as being those compounds which are metabolized into compounds of the general formula I in vivo. Typical prodrugs are phosphates, carbamates of amino acids, esters and others.

The preparation of the dibenzodiazepine derivatives I according to the invention has been outlined in Synthesis Scheme 1.

Scheme 1

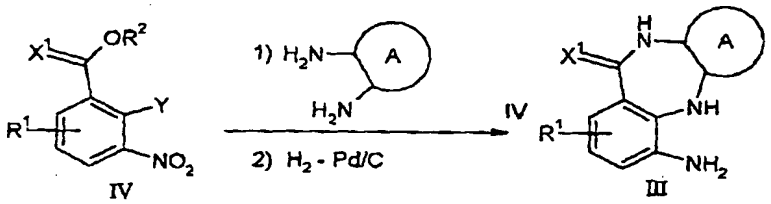


Condensation of the aldehyde II with diamines III results in the dibenzodiazepine I, with the reaction preferably being carried out in polar solvents, such as ethanol or dimethylformamide, in the added presence of

acids, such as acetic acid, at elevated temperature, as a rule 80-120°C. It is beneficial for the reaction if oxidizing agents, such as aqueous solutions of copper II salts, are added. The imine intermediate can also be oxidized using quinone derivatives.

The compounds III are synthesized, as shown in Scheme 2, by reacting a substituted nitrobenzoic ester IV, in which R^2 denotes branched or unbranched, saturated or unsaturated C_1-C_6-alkyl, with a suitable diamine in a polar solvent, such as for example dimethylformamide, in the presence of a base, such as potassium carbonate, at from 100°C to 150°C, preferably at from 110°C to 130°C, in particular at about 120°C, and subsequently hydrogenating in the presence of a suitable catalyst, such as 10% palladium on charcoal.

Scheme 2



Y = Halogen

The substituted dibenzodiazepine derivatives I which are contained in the present invention are inhibitors of the enzyme poly(ADP-ribose)polymerase or PARP (EC 2.4.2.30).

The inhibitory effect of the substituted dibenzodiazepine derivatives I can be determined using an enzyme test which is already known in the literature, with a K_i value being determined as the criterion of activity. In this way, the dibenzodiazepine derivatives I were assessed for their inhibitory effect on the enzyme poly(ADP-ribose)polymerase or PARP (EC 2.4.2.30).

The substituted dibenzodiazepine derivatives of the general formula I constitute inhibitors of poly(ADP-ribose)polymerase (PARP), or poly(ADP-ribose)synthase (PARS), as it is also termed, and can consequently be used for the treatment and prophylaxis of diseases which are associated with an increased activity of these enzymes.

The compounds of the formula I can be used for producing pharmaceuticals for treating damage following ischaemias, and for prophylaxis when ischaemias are expected in different organs.

The present dibenzodiazepine derivatives of the general formula I can accordingly be used for the treatment and prophylaxis of neurodegenerative diseases, and neuronal damage, particularly that which occurs following ischaemia, trauma, such as craniocerebral trauma, mass haemorrhages, subarachnoidal bleeding and stroke, and of neurodegenerative diseases, such as multiple infarction dementia, Alzheimer's disease and Huntington's disease, and of epilepsies, in particular of generalized epileptic seizures, such as petit mal and tonic-clonic seizures and partial epileptic seizures, such as temporal lobe, and complex-partial seizures, and, furthermore, for the treatment and prophylaxis of damage to the heart following cardiac ischaemias and damage to the kidneys following renal ischaemias, for example of acute renal insufficiency, of damage which is caused by medicinal therapies, such as in the case of cyclosporin treatment, of acute renal failure or of damage which occurs during and after a kidney transplantation. The compounds of the general formula I can furthermore be used for treating acute myocardial infarction and damage which occurs during and after its medicinal or mechanical lysis (for example using TPA, reteplase or streptokinase, or mechanically using a laser or rotablator) and microinfarctions, for example during and after heart

valve replacement, aneurysms and heart transplantations. The present dibenzodiazepine derivatives I can also be used for treating a revascularization of critically stenosed coronary arteries, for example in association with PCTA and bypass operations, and critically stenosed peripheral arteries, for example leg arteries. Furthermore, the dibenzodiazepine derivatives I can be of use for treating tumours and their metastases, and be used for treating immunological diseases, such as inflammations and rheumatic diseases, such as rheumatoid arthritis, and also for treating diabetes mellitus, for treating sepsis and multiorgan failure, for example in association with septic shock, and for treating ARDS (acute respiratory distress syndrome). In addition, the dibenzodiazepine derivatives I can be employed for treating viral diseases, in particular infections with retroviruses, such as HIV.

The pharmaceutical preparations according to the invention comprise a therapeutically effective quantity of the compounds I in addition to the customary pharmaceutical auxiliaries.

For local external use, for example in powders, ointments or sprays, the active compounds can be present at the customary concentration. As a rule, the active compounds are present in a quantity of from 0.001 to 1% by weight, preferably of from 0.001 to 0.1% by weight.

For internal use, the preparations are administered in single doses. In a single dose, from 0.1 to 100 mg are administered per kg of bodyweight. The preparations may be administered daily, in one or more doses depending on the nature and severity of the diseases.

In addition to the active compound, the pharmaceutical preparations according to the invention comprise the

customary carrier substances and diluents which are appropriate for the desired mode of administration. For local external use, it is possible to use auxiliary substances which are employed in the pharmaceutical industry, such as ethanol, isopropanol, ethoxylated castor oil, ethoxylated hydrogenated castor oil, polyacrylic acid, polyethylene glycol, polyethylene glycol stearate, ethoxylated fatty alcohols, paraffin oil, vaseline and lanolin. Lactose, propylene glycol, ethanol, starch, talc and polyvinylpyrrolidone are, for example, suitable for internal use.

Antioxidants such as tocopherol and butylated hydroxyanisole and butylated hydroxytoluene, taste-improving additives, stabilisers, emulsifiers and lubricants can also be present.

The substances which the preparation comprises in addition to the active compound, and also the substances which are used in producing the pharmaceutical preparations are toxicologically harmless and compatible with the given active compound. The pharmaceutical preparations are produced in a customary manner, for example by mixing the active compound with customary carrier substances and diluents.

The pharmaceutical preparations can be administered in a variety of modes of administration, for example perorally, parenterally, such as intravenously by means of infusion, subcutaneously, intraperitoneally and topically. Thus, possible preparation forms are tablets, emulsions, infusion and injection solutions, pastes, ointments, gels, creams, lotions, powders and sprays.

Pharmacological Example:

Inhibition of the enzyme poly(ADP-ribose)polymerase or PARP (EC 2.4.2.30)

A 96-well microtitre plate (Flacon) is coated with histones (Type II-AS; SIGMA H7755). For this, the histones are dissolved, to a concentration of 50 µg/ml, in carbonate buffer (0.05 M $NaHCO_3$; pH 9.4). The individual wells of the microtitre plates are incubated overnight with in each case 100 µl of this histone solution. After that, the histone solution is removed and the individual wells are incubated, at room temperature for 2 hours, with 200 µl of a 1% solution of BSA (bovine serum albumin) in carbonate buffer. The plates are then washed three times with washing buffer (0.05% Tween 10 in PBS). For the enzyme reaction, 50 µl of the enzyme reaction solution (5 µl of reaction buffer (1M Tris-HCl, pH 8.0, 100 mM $MgCl_2$, 10 mM DTT), 0.5 µl of PARP (c = 0.22 µg/µl), 4 µl of activated DNA (SIGMA D-4522, 1 mg/ml in water), 40.5 µl of H_2O) are preincubated, per well, for 10 minutes with 10 µl of an inhibitor solution. The enzyme reaction is started by adding 40 µl of a substrate solution (4 µl of reaction buffer (see above), 8 µl of NAD solution (100 µM in H_2O), 28 µl of H_2O). The reaction time is twenty minutes at room temperature. The reaction is stopped by washing three times with washing buffer (see above). The plate is subsequently incubated for one hour, at room temperature, with a specific anti-poly-ADP-ribose antibody. The antibody employed was a monoclonal "10H" anti-poly(ADP-ribose)antibody (Kawamaitsu H et al. (1984) Monoclonal antibodies to poly(adenosine diphosphate ribose) recognize different structures. Biochemistry 23, 3771-3777). Polyclonal antibodies can also be used.

The antibodies were employed in a 1:5000 dilution in antibody buffer (1% BSA in PBS; 0.05% Tween 20). After the plate had been washed three times with washing buffer, there then followed a one-hour incubation, at room temperature, with the secondary antibody. In this case, a peroxidase-coupled anti-mouse IgG (Boehringer

Mannheim) was used for the monoclonal antibody and a peroxidase-coupled anti-rabbit IgG (SIGMA A-6154) was used for the rabbit antibody, in each case in a 1:10,000 dilution in antibody buffer. After the plate had been washed three times with washing buffer, the colour reaction was then carried out, at room temperature for approx. 15 min, using 100 µl of colour reagent (SIGMA, TMB readymix, T8540)/well. The colour reaction is stopped by adding 100 µl of 2M H_2SO_4. After that, measurement takes place immediately (450 nm as against 620 nm; "Easy Reader" ELISA plate reader EAR340AT, SLT-Labinstruments, Austria). The IC50 value of an inhibitor which is being measured is the concentration of the inhibitor at which there is a half-maximum change in colour concentration.

Examples

Example 1
1-Phenylbenzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7*H*)-one

a) 4-Nitro-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one

18 g of methyl 2-chloro-3-nitrobenzoate, 35 g of 1,2-diaminobenzene and 23 g of potassium carbonate are heated to reflux for 4 hours in 400 ml of dimethylformamide. After the reaction has been completed, the reaction mixture is stirred into 2 l of water. The resulting precipitate is separated off by filtration, washed with water and dried in a vacuum-drying oven. 11.1 g of product are obtained.

b) 4-Amino-5,10-dihydro-11*H*-dibenzo[*b*, *e*][1,4]diazepin-11-one dihydrochloride

11 g of the 1a product are initially introduced into 800 ml of dimethylformamide and hydrogenated in the presence of 1 g of 10% Pd on charcoal. After the reaction has come to an end, the catalyst is removed by filtration. The filtrate is concentrated in vacuo. 50 ml of 6M isopropanolic hydrochloric acid are added, at boiling heat, to a solution of the residue. The crop of crystals which is obtained following cooling is separated off by filtration and dried in a vacuum-drying oven. 10 g of product are obtained.

c) 1-Phenylbenzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7*H*)-one

A solution of 1.5 g of the 1b product and 0.8 g of sodium acetate in 120 ml of methanol is stirred at room temperature for 30 min. Glacial acetic acid is added to the solution, after which a solution of 0.7 g of benzaldehyde in 25 ml of methanol is added dropwise. The reaction mixture is heated to reflux for 3 hours. After the mixture has been cooled down, a solution of 1.5 g of copper II acetate in 100 ml of water is added dropwise. The reaction mixture is heated to reflux for 2 hours. After the reaction has come to an end, the mixture is poured onto 100 ml of ammonia water. The product is extracted with ethyl acetate. After the solvent has been removed in vacuo, the crude product is purified by silica gel chromatography. 0.52 g of product is obtained.

^{1}H NMR (D_6-DMSO): δ = 6.6 (1H), 6.9 (1H), 7.3-8.0 (9H), 10.3 (1H).

Example 2

1-[4-(4-Methylpiperazin-1-yl)phenyl]benzo[*b*]imidazo-[4,5,1-*jk*][1,4]benzodiazepin-6(7*H*)-one

The product is obtained from 4-amino-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one dihydrochloride and 4-(4-methylpiperazin-1-yl)benzaldehyde in analogy with the directions in 1c.

^{1}H NMR (D_6-DMSO): δ = 2.2 (3H), 2.45 (2H), 3.25 (2H), 6.7-8.9 (11H), 10.3 (1H).

Example 3
1-{4-[2-N,N-Diethylaminoeth-1-yloxy]phenyl}benzo-[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7*H*)-one

The product is obtained from 4-amino-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one dihydrochloride and 4-[2-N,N-diethylaminoeth-1-yloxy]benzaldehyde in analogy with the directions in 1c.

^{1}H NMR (D_6-DMSO): δ = 0.95 (6H), 2.55 (4H), 2.8 (2H), 4.1 (2H), 6.7 (1H), 6.9 (1H), 7.0-8.0 (9H), 10.3 (1H).

Example 4
1-[4(1*H*-Imidazol-1-yl)phenyl]benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7*H*)-one

The product is obtained from 4-amino-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one dihydrochloride and 4-(1*H*-imidazol-1-yl)benzaldehyde in analogy with the directions in 1c.

^{1}H NMR (D_6-DMSO): δ = 6.7 (1H), 6.9 (1H), 7.15 (1H), 7.2 (1H), 7.4 (1H), 7.45 (1H), 7.8-8.0 (7H), 8.45 (1H), 10.3 (1H).

Example 5
1-(1-*n*-Propylpiperidin-4-yl)benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7*H*)-one

The product is obtained from 4-amino-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one dihydrochloride and 1-

n-propylpiperidine-4-carboxaldehyde in analogy with the directions in 1c.

^{1}H NMR (D_6-DMSO): δ = 0.9 (3H), 1.7 (2H), 2.2-2.4 (4H), 2.9-3.2 (4H), 3.55 (2H), 3.7 (1H), 7.2-7.5 (5H), 7.9 (2H), 10.2 (1H), 10.8 (1H).

Example 6
1-Indol-3-ylbenzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

The product is obtained from 4-amino-5,10-dihydro-11*H*-dibenzo[*b*,*e*][1,4]diazepin-11-one dihydrochloride and indole-3-carboxaldehyde in analogy with the directions in 1c.

^{1}H NMR (D_6-DMSO): δ = 6.85 (1H), 7.0 (1H), 7.1 (1H), 7.2 (2H), 7.4 (2H), 7.5 (1H), 7.8 (2H), 7.9 (2H), 10.25 (1H).

The following compounds according to the invention can be prepared in analogy with the above-described method:

1. 1-(4(4-*n*-Propylpiperazin-1-yl)phenyl)benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

2. 1-(4(4-Isopropylpiperazin-1-yl)phenyl)benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

3. 1-(4(4-Benzylpiperazin-1-yl)phenyl)benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

4. 1-(4(4-*n*-Butylpiperazin-1-yl)phenyl)benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

5. 1-(4(4-Ethylpiperazin-1-yl)phenyl)benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

6. 1-(4(2-N,N-Dimethylaminoeth-1-yloxy)phenyl)benzo-[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

7. 1-(4-(2-Pyrrolidin-1-yleth-1-yloxy)phenyl)-benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

8. 1-(4-(2-Piperazin-1-yleth-1-yloxy)phenyl)-benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

9. 1-(4-(2-(4-Methylpiperazin-1-yl)eth-1-yloxy)phenyl)-benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

10. 1-(4-(2-(4-Propylpiperazin-1-yl)eth-1-yloxy)phenyl)-benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

11. 1-(4-(2-(4-Ethylpiperazin-1-yl)eth-1-yloxy)phenyl)-benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

12. 1-(4-(2-(4-Benzylpiperazin-1-yl)eth-1-yloxy)phenyl)-benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

13. 1-(4-(2-(4-Acetamidopiperazin-1-yl)eth-1-yloxy)phenyl)-benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

14. 1-(4-(2-(4-Benzamidopiperazin-1-yl)eth-1-yloxy)phenyl)-benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

15. 1-(4(4-Methylhomopiperazin-1-yl)phenyl)-benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

16. 1-(4(4-Benzylhomopiperazin-1-yl)phenyl)-benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

17. 1-(4(4-*n*-Butylhomopiperazin-1-yl)phenyl)-benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

18. 1-(4(4-Ethylhomopiperazin-1-yl)phenyl)-benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

19. 1-(4(Pyrrol-1-yl)phenyl)-benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

20. 1-(4(3-Aminomethylpyrrol-1-yl)phenyl)-benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

21. 1-(3(3-Aminomethylpyrrol-1-yl)phenyl)-benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

22. 1-(4(3-Trifluoroacetamidomethylpyrrol-1-yl)phenyl)-benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

23. 1-(4(2-Aminomethylpyrrol-1-yl)phenyl)-benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

24. 1-(4(3-Formylpyrrol-1-yl)phenyl)-benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

25. 1-(4-Methoxyphenyl)benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

26. 1-(4-Chlorophenyl)benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

27. 1-(4-Aminophenyl)benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

28. 1-(4-Isopropylphenyl)benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

29. 1-(3-Chlorophenyl)-5,6-dihydroimidazo[4,5,1-*jk*][1,4]benzodiazepin-7(4H)-one

30. 1-(3-Methylphenyl)benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

31. 1-(3-Phenylphenyl)benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

32. 1-(3-Isopropylphenyl)benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

33. 1-(3-Fluorophenyl)benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

34. 1-Piperidin-4-ylbenzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

35. 1-(1-Ethylpiperidin-4-ylbenzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

36. 1-(1-Isopropylpiperidin-4-ylbenzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

37. 1-Pyridin-4-ylbenzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

38. 1-Pyridin-3-ylbenzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

39. 1-Pyridin-2-ylbenzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

40. 1-[6-(1*H*-Imidazol-1-yl)pyridin-3-yl]benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

41. 1-[6-(2-N,N-Dimethylamino-eth-1-ylmethylamino) pyridin-3-yl]benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

42. 1-[6-(Pyrrol-1-yl)pyridin-3-yl]benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

43. 1-[6-(3-Aminomethylpyrrol-1-yl)pyridin-3-yl]benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

44. 1-[6-(4-Methylpiperazin-1-yl)pyridin-3-yl]benzo[*b*]imidazo[4,5,1-*jk*][1,4]benzodiazepin-6(7H)-one

45. 1-Thien-2-ylbenzo[b]imidazo[4,5,1-jk][1,4]benzodiazepin-6(7H)-one

46. 1-Indol-5-ylbenzo[b]imidazo[4,5,1-jk][1,4]benzodiazepin-6(7H)-one

47. 1-Indol-2-ylbenzo[b]imidazo[4,5,1-jk][1,4]benzodiazepin-6(7H)-one

48. 1-Quinolin-3-ylbenzo[b]imidazo[4,5,1-jk][1,4]benzodiazepin-6(7H)-one

49. 1-Isoquinolin-3-ylbenzo[b]imidazo[4,5,1-jk][1,4]benzodiazepin-6(7H)-one

50. 1-Quinoxalin-2-ylbenzo[b]imidazo[4,5,1-jk][1,4]benzodiazepin-6(7H)-one

51. 1-Naphth-2-ylbenzo[b]imidazo[4,5,1-jk][1,4]benzodiazepin-6(7H)-one

52. 1-(2-N,N-Dimethylaminoeth-1-ylamino)phenyl)benzo[b]imidazo[4,5,1-jk][1,4]benzodiazepin-6(7H)-one

53. 1-(2-N,N-Diethylaminoeth-1-ylamino)phenyl)benzo[b]imidazo[4,5,1-jk][1,4]benzodiazepin-6(7H)-one

54. 1-(2-Piperidin-1-yleth-1-ylamino)phenyl)benzo[b]imidazo[4,5,1-jk][1,4]benzodiazepin-6(7H)-one

55. 1-(2-Pyrrolidin-1-yleth-1-ylamino)phenyl)benzo[b]imidazo[4,5,1-jk][1,4]benzodiazepin-6(7H)-one

56. 1-(3-N,N-Dimethylaminoprop-1-ylamino)phenyl)benzo[b]imidazo[4,5,1-jk][1,4]benzodiazepin-6(7H)-one

57. 1-(3-N,N-Diethylaminoprop-1-ylamino)phenyl)benzo[b]imidazo[4,5,1-jk][1,4]benzodiazepin-6(7H)-one

58. 1-(3-Piperidin-1-ylprop-1-ylamino)phenyl)benzo[b]imidazo[4,5,1-jk][1,4]benzodiazepin-6(7H)-one

59. 1-(3-Pyrrolidin-1-ylprop-1-ylamino)phenyl)benzo[b]imidazo[4,5,1-jk][1,4]benzodiazepin-6(7H)-one

60. 1-Cylcohexylbenzo[b]imidazo[4,5,1-jk][1,4]benzodiazepin-6(7H)-one

61. 1-(cis-4-Aminocyclohex-1-yl)benzo[b]imidazo[4,5,1-jk][1,4]benzodiazepin-6(7H)-one

62. 1-(4-Methoxycyclohex-1-yl)benzo[b]imidazo[4,5,1-jk][1,4]benzodiazepin-6(7H)-one

63. 1-(3-Aminophenyl)benzo[b]imidazo[4,5,1-jk][1,4]benzodiazepin-6(7H)-one

64. 1-(4-N,N-Diethylaminomethylphenyl)benzo-[b]imidazo[4,5,1-jk][1,4]benzodiazepin-6(7H)-one

65. 1-(4-(2-N,N-Diethylaminoeth-1-yl)phenyl)benzo[b]imidazo[4,5,1-jk][1,4]benzodiazepin-6(7H)-one

66. 1-(4-Hydroxyphenyl)benzo[b]imidazo[4,5,1-jk][1,4]benzodiazepin-6(7H)-one

67. 1-(4-Pyrrolidinemethylphenyl)benzo[b]imidazo-[4,5,1-jk][1,4]benzodiazepin-6(7H)-one

68. 1-(2-Methylthiophenyl)benzo[b]imidazo[4,5,1-jk][1,4]benzodiazepin-6(7H)-one

69. 1-(4-Carboxyphenyl)benzo[b]imidazo[4,5,1-jk][1,4]benzodiazepin-6(7H)-one

70. 1-(3,5-bis(Trifluoromethyl)phenyl)benzo[b]imidazo[4,5,1-jk][1,4]benzodiazepin-6(7H)-one

71. 1-(4-tert-Butylphenyl)benzo[b]imidazo[4,5,1-jk][1,4]benzodiazepin-6(7H)-one

72. 1-(3-(Morpholin-4-ylmethyl)phenyl) benzo[b]imidazo[4,5,1-jk][1,4]benzodiazepin-6(7H)-one